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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/914,454	01/14/2002	Guido Grandi	PP01591.101	4170

7590 01/11/2006
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EXAMINER

MINNIFIELD, NITA M

ART UNIT PAPER NUMBER

1645

DATE MAILED: 01/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/914,454	GRANDI ET AL.	
	Examiner	Art Unit	
	N. M. Minnifield	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 03 October 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-6,8-21,23-25,27-39 and 43-45 is/are pending in the application.
- 4a) Of the above claim(s) 27-39 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-6,8-21,23-25 and 43-45 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☒ Claim(s) 27-39 are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Response to Amendment

1. Applicants' amendment filed October 3, 2005 is acknowledged and has been entered. Claims 7, 22, 26 and 40-42 have been canceled. Claims 1, 8, 9 and 23 have been amended. Claims 1-6, 8-21, 23-25, 27-39 and 43-45 are now pending in the present application. All rejections have been withdrawn in view of Applicants' amendment to the claims and/or comments, with the exception of those discussed below.
2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
3. This application contains claims 27-39 have been drawn to an invention nonelected with traverse in the paper filed January 24, 2005. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.
4. The Examiner acknowledges Applicants' request for rejoinder of methods claims once the product claims have been deemed allowable. In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim

is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See “Guidance on Treatment of Product and Process Claims in light of *In re Ochiai*, *In re Brouwer* and 35 U.S.C. § 103(b),” 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.** Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the examiner before the patent issues withdraws the restriction requirement. See MPEP § 804.01.

5. Claims 1-3, 6, 8, 15-21, 23 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Krieg et al (WO 98/18810) in view of Schwartz et al (WO 98/55495).

Krieg et al teaches that CpG oligonucleotides are immunostimulatory and are useful as synthetic adjuvants (abstract; p. 1; claims). Krieg et al teaches that the oligonucleotides can be used to treat, prevent or ameliorate disorders that include bacterial infection (p. 10). The infectious bacteria include *Neisseria gonorrhoeae* and *Neisseria meningitidis* (p. 17). The prior art teaches that the oligonucleotide can have a phosphorothioate bond (p. 22). “Nonspecific simulators of the immune response are known as adjuvants. The use of adjuvants is essential to induce a strong antibody response to soluble antigens (reference omitted). The overall effect of adjuvants is dramatic and their importance cannot

be overemphasized. The action of an adjuvant allows much smaller doses of antigen to be used and generates antibody responses that are more persistent. The nonspecific activation of the immune response often can spell the difference between success and failure in obtaining an immune response. Adjuvants should be used for first injections unless there is some very specific reason to avoid this.” (p. 33, l. 30-38) Krieg et al teach the claimed SEQ ID NO: 1. “Recently an intense drive to find potent adjuvants with more acceptable side effects has led to the production of new synthetic adjuvants. The present invention provides the sequence 1826 TCCATGACGTTCTGACGTT (SEQ ID NO: 10), which is an adjuvant including CpG containing nucleic acids. The sequence is a strong immune activating sequence and is a superb adjuvant, with efficacy comparable or superior to complete Freund’s, but without apparent toxicity.” (p. 34, l. 15-20) Krieg et al teaches the use of additional adjuvants in the composition. “Immunostimulatory oligonucleotides and unmethylated CpG containing vaccines, which directly activate lymphocytes and co-stimulate an antigen-specific response, are fundamentally different from conventional adjuvants (e.g. aluminum precipitates), which are inert when injected alone and are thought to work through absorbing the antigen and thereby presenting it more effectively to immune cells. Further, conventional adjuvants only work for certain antigens, only induce an antibody (humoral) immune response (Th2), and are very poor at inducing cellular immune responses (Th1). For many pathogens, the humoral response contributes little to protection, and can even be detrimental.” (p. 65, l. 1-8) Krieg et al teaches the claimed invention except for the specific additional adjuvants.

However, Schwartz et al teaches a composition comprising an immunostimulatory oligonucleotide (CpG) and antigen (abstract). Schwartz et al

teaches that the antigen can be protein, glycoproteins, polysaccharides and lipids (p. 4, l. 33-34; p. 12, l. 9-28; pp. 12-13). “In another embodiment, the immunomodulatory composition comprises an oligonucleotide that contains at least one immunostimulatory (ISS) octanucleotide and a facilitator selected from the group consisting of co-stimulatory molecules, cytokines, chemokines, targeting protein ligand, a trans-activating factor, a peptide, and a peptide comprising a modified amino acid.” (p. 4, l. 36-39; p. 12, l. 9-28) Schwartz et al teaches that the composition can also comprise the oligonucleotide, an antigen and an adjuvant (p. 5, l. 1-2; p. 8, l. 19-23). The adjuvants include alum, lipid emulsions and polylactide/polyglycolide microparticles as well as oil-in-water emulsions, mycobacterium cell wall preparations and muramyl peptide (p. 12; pp. 15-19; claims). Schwartz et al teaches that the compositions provide for methods of treating subjects in need of immune modulation; the subjects may be suffering from infectious diseases and bacterial infections (p. 5; claims). Schwartz et al teaches that the CG motif be flanked by two purines immediately 5’ to said motif and two pyrimidines immediately 3’ to said motif (p. 7, l. 14-21). Schwartz et al teaches that an immunomodulatory facilitators, molecules which support and/or enhance the immunomodulatory activity of an oligonucleotide, can be used in the composition, which include cytokines and/or adjuvants (p. 14, l. 15-36), as well as compositions comprising an oligonucleotide, antigen and adjuvant (claims).

In view of the combined teachings of Krieg et al and Schwartz et al it would have been obvious to a person of ordinary skill in the art to prepare a composition that comprises a CG oligonucleotide and a *Neisseria* antigen and optionally another adjuvant. The prior art teaches that the *Neisseria* antigen can be *Neisseria meningitidis* or *Neisseria gonorrhoeae* and an adjuvant composition comprising an

oligonucleotide comprising at least one CG motif. Krieg et al teaches the claimed oligonucleotide as set forth in SEQ ID NO: 1 and teaches that it is a strong immune activating sequence and is a superb adjuvant. Both references teach the use of multiple adjuvants in the compositions. Schwartz et al teaches that the specifically claimed additional adjuvants can be used in the compositions to enhance the immunomodulatory activity. The prior art does not specifically teach the claimed diameter of the oil droplets or the ratio of oil droplets and emulsifying agents. However, it would have been obvious to one having ordinary skill in the art at the time the invention was made to determine the diameter size and ratios, since it has been held that discovering an optimum value of a result effective variable involves only routine skill in the art. *In re Boesch*, 617 F.2d 272, 205 USPQ 215 (CCPA 1980). The prior art teaches that the compositions can be used to treat infection in a subject. The claimed invention is prima facie obvious in view of the combination of teachings as a whole found in Krieg et al and Schwartz et al, absent any convincing evidence to the contrary.

The rejection is maintained for the reasons of record. Applicant's arguments filed October 3, 2005 have been fully considered but they are not persuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicants have asserted that Schwartz et al fails to cure the deficiencies of Krieg et al and that Schwartz et al does not specifically teach or suggest oil-in-water emulsions, wherein at least 80% of the oil droplets are less

than 1 micron in diameter. The Examiner notes that the prior art does not specifically teach the claimed diameter of the oil droplets or the ratio of oil droplets and emulsifying agents. However, it would have been obvious to one having ordinary skill in the art at the time the invention was made to determine the diameter size and ratios, since it has been held that discovering an optimum value of a result effective variable involves only routine skill in the art. *In re Boesch*, 617 F.2d 272, 205 USPQ 215 (CCPA 1980). The prior art taken as a whole teaches the claimed invention absent any convincing evidence to the contrary.

6. Claims 1-6, 8-21, 23-25 and 43-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Agrawal et al (WO 98/49288) in view of Fraser et al (WO/99/57280).

Agrawal et al teaches a composition comprising a *Neisseria* antigen and a adjuvant composition comprising an oligonucleotide comprising at least one CG motif. The prior art teaches that the compositions can be used for methods for prophylactically protect a mammal from infection by a pathogen (p. 4). Agrawal et al teaches that pathogens include *Neisseria* spp. (p. 12). Agrawal et al teaches an oligonucleotide that has at least one CG motif and it has at least one phosphorothioate bond (see p. 5; p. 10). Agrawal et al teaches that the CG motif be flanked by two purines immediately 5' to said motif and two pyrimidines immediately 3' to said motif (see p. 11). Agrawal et al teaches that the oligonucleotide should be formulated in a physiologically acceptable carrier or diluent, including without limitation saline and/or an adjuvant (pp. 8-9). Agrawal et al teaches the claimed invention except for the specific *Neisseria* protein set forth in claimed SEQ ID NO: 31.

However, Fraser et al teaches antigens of *Neisseria meningitidis* serogroup B and *Neisseria gonorrhoeae* as well as amino acid sequences to the antigens and that they can be used in compositions (p. 4-5; p. 7; p. 134; p. 8). Claimed SEQ ID NO: 31 is found on p 134 of Fraser et al (also see attached sequence search printout). Fraser et al teaches that the compositions can comprise adjuvants and other components that promote or enhance the antigen (pp. 32-33; p. 34). Fraser et al disclose oil droplets as well as adjuvants such as aluminum salts, oil-in-water emulsion formulations that contains 5% squalene or 10% (i.e. oil) and 0.5% or 0.4% Tween 80 (i.e. emulsifying agent), saponin adjuvants, complete Freund's adjuvant, incomplete Freund's adjuvant and muramyl peptides (pp. 35-36).

In view of the combined teachings of Agrawal et al and Fraser et al it would have been obvious to a person of ordinary skill in the art to prepare a composition comprising a *Neisseria* antigen (*Neisseria meningitidis* serogroup B and *Neisseria gonorrhoeae*) and an adjuvant composition comprising an oligonucleotide comprising at least one CG motif. Agrawal et al teaches the claimed oligonucleotide as set forth in SEQ ID NO: 1 and teaches that it has adjuvant or immunostimulating properties as well as the fact that Agrawal et al teaches treating bacterial infections and disease. Both references teach the use of multiple adjuvants in the compositions. Fraser et al teaches the specific antigen of *Neisseria* claimed by Applicants set forth in SEQ ID NO: 31 and teaches that all of these antigens can be used in vaccine, pharmaceutical and therapeutic compositions. The prior art does not specifically teach the claimed diameter of the oil droplets or the ratio of oil droplets and emulsifying agents. However, it would have been obvious to one having ordinary skill in the art at the time the invention was made to determine the diameter size and ratios, since it has been held that discovering an

optimum value of a result effective variable involves only routine skill in the art. *In re Boesch*, 617 F.2d 272, 205 USPQ 215 (CCPA 1980). The claimed invention is prima facie obvious in view of the combination of teachings as a whole found in Agrawal et al and Fraser et al, absent any convincing evidence to the contrary.

The rejection is maintained for the reasons of record. Applicant's arguments filed October 3, 2005 have been fully considered but they are not persuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicants have asserted that Fraser et al fails to cure the deficiencies of Krieg et al and that Agrawal et al does not specifically teach or suggest oil-in-water emulsions, wherein at least 80% of the oil droplets are less than 1 micron in diameter. It is noted that Fraser et al does in fact teach the use of oil-in-water emulsions and emulsifying agents. The Examiner notes that the prior art does not specifically teach the claimed diameter of the oil droplets or the ratio of oil droplets and emulsifying agents. However, it would have been obvious to one having ordinary skill in the art at the time the invention was made to determine the diameter size and ratios, since it has been held that discovering an optimum value of a result effective variable involves only routine skill in the art. *In re Boesch*, 617 F.2d 272, 205 USPQ 215 (CCPA 1980). The prior art taken as a whole teaches the claimed invention absent any convincing evidence to the contrary.

7. No claims are allowed.

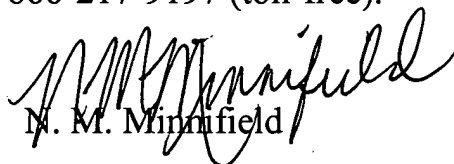
8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to N. M. Minnifield whose telephone number is 571-272-0860. The examiner can normally be reached on M-F (8:00-5:30) Second Friday Off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette R.F. Smith can be reached on 571-272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

A handwritten signature in black ink, appearing to read 'N. M. Minnifield', is written over the printed name.

N. M. Minnifield

Primary Examiner

Art Unit 1645

NMM

January 9, 2006